Participants:
Ray Anton, Medical University of South Carolina, Chair
Sarah Akerman, Alkermes
Arnie Aldridge, RTI
Henri-Jean Aubin, Hôpitaux Universitaires Paris-Sud
Dan Falk, NIAAA
Deborah Hasin, Columbia University
Robert Hofbauer, Mitsubishi Tanabe Pharma
Henry Kranzler, University of Connecticut Health Center
Raye Litten, NIAAA
Didier Meulien, Lundbeck
Roger Meyer, Penn State Hershey College of Medicine
Martin Mumenthaler, Alkermes
Stephanie O’Malley, Yale University School of Medicine
Tanya Ramey, NIDA
Katie Witkiewitz, University of New Mexico
Lindsay Snyder, Parthenon Management Group

Summary of the Meeting:
1. New members and guests were welcomed to the meeting.

2. K. Witkiewitz provided an update on the WHO drinking level change in stability over time, as well as the concept of how severity could affect this sustainability. ACTION ITEMS: The group agreed to the following next steps:

   Using other data sets that have a wider range of AUD severity available publicly to repeat some of the WHO analyses. Also consider other ways to measure severity in the clinical trial data sets available to ACTIVE including sleep and number of DSM Symptoms.

3. A. Aldridge provided an update on the workgroup paper on WHO drinking level change and economic issues in the COMBINE trial, including an update on the review process. ACTION ITEM: The group will request NIAAA contacts to review the paper and make a recommendation on the appropriate journal. An updated draft within the next week to circulate to ACTIVE group.

4. A discussion on the AAAP 2018 Meeting presentation. In general, the presentation was very well received. The group discussed the Alcohol Abstinence Questioned as Addiction Treatment Goal article reported from the ACTIVE’s AAAP 2018 Meeting leading to a letter published in ASAM news. ACTION ITEM: The group discussed submitting a symposium abstract for the ASAM 2020 Meeting in Denver, Colorado, and suggested that R. Meyers might chair the session.

5. R. Anton and R. Litten led a discussion and overview of the initial meeting with the FDA Critical Path Innovation Meeting (CPIM) Meeting on November 09, 2018. The group is currently waiting on the FDA’s response to the additional documents that were submitted in January 2019; the anticipated response date is early April 2019. FUTURE ITEMS: It was noted that while it was not the primary goal of the initial meeting and dossier material to address “AUD clinical trial length” issues, it was logically difficult to disassociate trial length from outcome variable since they are confounded. While, it was generally accepted that the data, so far, suggested that a trial length of perhaps 4 months was ideal from a feasibility and practicality point of view (e.g. acceptable dropout rate) as well as a WHO shift.
stabilization metric, there was general agreement to wait until the April response from the FDA to consider additional information as supplements on this trial length issue. The group discussed that although K. Witkiewitz’s newer WHO shift stability information is not included in the initial dossier; after the FDA April response, the group would consider providing supplementary information regarding longer term stability if requested.

6. **Review/Highlights of NESARC – WHO Shift Data – New Findings:** D. Hasin reviewed the WHO Drinking Risk Levels & Alcohol Consequences NESARC Waves 1 and 2, NESARC-III topics (partly in response to queries at the AAP presentation). **ACTION ITEM:** D. Hasin will run outcomes for the binary WHO drinking level measure as defined by K. Witkiewitz and resend all tables next week to the group to review. D. Hasin might also look for NHANES data from the CDC to see if drinking data are sufficient to triangulate on change in health outcomes/conditions. **ACTION ITEM:** R. Anton brought up that one issue raised by the ASAM letter was that drinking levels at different ages might mean different things for AUD diagnosis and the value of the WHO shift measure. This suggested that in addition to testing whether results were modified by a diagnosis of alcohol dependence, that age (e.g., younger and older than 40) might modify the results as well. D. Hasin said these could be tried. **ACTION ITEM:** D. Hasin agreed to conduct these analyses, and also to examine the distribution of mean ETOH/day in NESARC-III data to begin a replication of her initial NESARC-II WHO category paper. The group felt this would be a strong publication if it replicates the initial published work and would solidify the concept of WHO risk drinking levels being clinically relevant.

7. **Highlights of WHO Drinking Level Change Stability Over Time and Other New Data on Severity:** K. Witkiewitz discussed the specific AUD Severity question from COMBINE Study data stating: “Severity of alcohol dependence for the worst week of the past month” and the outcomes were as follows:

   - **Mild:** mean 4 DSM-IV dependence symptoms
   - **Moderate:** mean 5.5 DSM-IV dependence symptoms
   - **Severe:** mean 6.5 DSM-IV dependence symptoms

   **ACTION ITEM:** K. Witkiewitz agreed to look at consumption and WHO risk drinking category levels of mild, moderate and severe and remove abstainers, and they further evaluate stability over time. The group agreed to look at drafting a paper for importance in reduction benefits, even if it’s abstinence.

8. **Continuation of FDA Response:** R. Anton and R. Litten led discussion on the FDA response after reviewing Thursday’s presentations. The group discussed the following topics:

   - **Qualifying the timeline follow back:** The group discussed that it needs to be acceptable as a method to collect that data used as outcome measure. The FDA possibly could provide an instructional set in the guidelines of how to use the timeline follow back.
   - **EMA & Similar International Agencies:** The group agreed that the EMA should be fully apprised of the ACTIVE work with the FDA, possibly including the dossier provided to them. The goal is to be assured that the agencies have similar knowledge with the hope of a consistent outcome measure be adopted by both the EMA and FDA. The following link allows individuals to submit scientific research development to be reviewed and advised by the EMA:


   **ACTION ITEM:** R. Anton (copying to Karl Mann, HJ. Aubin, and D. Meulien) will contact the ACTIVE EMA representative, Michael Buehlen, next week to seek appraise him of the ACTIVE progress and ask his opinion on next steps regarding FDA and EMA harmonization. HJ. Aubin noted that the EMA guidelines for AUD clinical trials are about 10 years old and at the time they had very little data to support the WHO shift measure incorporated in the guideline. He wondered if they would be open to a paper addressing the EMA guidelines, their limitations and advantages and using the published WHO shift data to support another look at the guideline? R. Anton agreed to include that in the letter to the EMA representative as well but pointed out we do not want to get too far ahead of the FDA discussions either.
9. **Treatment Response “Stability”:** D. Falk discussed four ways to operationalize and evaluate stability of response to treatment:
   a. Agreement (kappa) of Early response with Later response
   b. Agreement (i.e., kappas) of response between Consecutive months (Witkiewitz et al., 2017)
   c. Prevalence of monthly response patterns across treatment
   d. Compare responses at end of treatment (e.g., 3- vs 6-months) with long term follow-up response

The group discussed that it may be beneficial to further discuss the duration of the trial issue and also the role of adaptive design, re-randomization and discontinuation studies.

**ACTION ITEM:** K. Witkiewitz will pull the Stability of WHO out to a year in the RREP and UKATT datasets and send to group.

**ACTION ITEM:** The group agreed to pull together a summary sheet to summarize the stability data in case across studies in case they are required by, or can further inform, the FDA process. The group agreed to present the data separately based on trial duration, because most trials were conducted in 3-4 months, but now some data is available for 6 months trials (e.g. recent NIAAA gabapentin study).

10. **Future ACTIVE Considerations:** The group discussed the following future items:
   a. Use of Biomarkers in Clinical Trials: The group agreed it would be interesting to look at data for %CDT and PEth biomarkers and other predictive tests such as pharmacogenetics, neuroimaging, self-reporting with reward and relief drinking as a different way of phenotyping.
   b. Adaptive Designs: The group discussed that there are trials using adaptive design including trials with methamphetamine that could provide examples for AUD.
   c. Dual Diagnosis Considerations – psychiatric & alcohol: The group discussed naltrexone being used in patients with psychiatric disorders, as well as if there is a way to open up inclusion criteria for a broader range of other symptoms. Does it make sense to open up inclusion criteria to include depressed individuals or those with other diagnoses (e.g. PTSD, Bipolar etc.)? As in the past, members pointed to the increased difficulty of dual-diagnoses trials both in recruitment but also in retention and interpretation. Generally, this should be dissuaded at this time.
   d. Power Gain or Lost in Multisite Trials – Does N of sites matter? It would improve medications development for AUD if a method could be developed to figure out the appropriate number of sites that should be included in an AUD trial. The next step is to find how much variation and correlation is needed for the number of patients, dropouts, and sites. For dichotomous outcomes, need to have a certain number of events (people that achieve a dichotomous outcome) per site or need to combine sites. Does affect size differ for single site versus multi sites? There is also the issue of pilot studies and if they are worthwhile; are they a stable and predictive enough effect size? There seemed to be general agreement that this be kept as a potential focus for the ACTIVE group in the future.
   e. Personalized Medicine: Everyone that collects data has the same problem with small treatment effects unless there is sub groups that are found. Drug companies prefer broad range of approval and cross cultural drinking patterns exist, but a more targeted developmental approach might be more successful. This might be considered by ACTIVE going forward.
   f. PRO & Craving Measures: **ACTION ITEM:** S. O’Malley will set up meeting with Elektra Papadopoulos, FDA, regarding the PRO and craving measures to see if she thinks 1) what should ACTIVE do to make acceptable outcome that can go into a label regarding promise measures as PROs and 2) what happens if the FDA accepts it and what more do we need to do if it gets accepted?

11. **Discussion of Future Papers, Presentations, and Industry Suggestions:** The group discussed future papers and presentations:
   a. Papers
      i. K. Witkiewitz:
1. First Priority: Severity paper
2. Looking at maintenance of 3-year Project Match and COMBINE data, as well as the severity for 3-year paper
   ii. A. Aldridge and Gary Zarkin; WHO shift and health care cost paper.
   iii. D. Hasin and group: Replication of original WHO risk drinking category and consequences paper using the NESARC-3 data.
   iv. H. Kranzler: Topiramate paper to report outcomes in the topiramate study with and without phenotypes using WHO severity level change. Dr. Anton will also evaluate in a recent gabapentin trial. ACTIVE publications should be referenced in those papers.
   v. Paper for importance in reduction benefits, even if it isn’t abstinence
   vi. Paper on benefits of using PROMISE
   vii. Summary paper of WHO shift findings, if FDA agrees to incorporate in its guidelines.

b. Meeting Presentations
   i. ASAM 2020 Meeting: April 2-5, 2020 in Denver, Colorado.
      1. Primary Deadlines for 2019: The first abstract submission period is for poster presentation, focus session, and workshop session submissions. This period was open from **August 13, 2018 through October 14, 2018**.
   ii. ASCP 2020 Meeting: May 26-29, 2020 in Miami Beach, Florida.
      2. Topic: Symposium of clinical lab studies. How a drug is working and what type of patients are you recruiting, including looking at paradigms and patients that you recruit. If positive FDA decision perhaps summary of WHO findings, sustainability and severity issues might be presented.

c. Industry Suggestions: The industry participants discussed learning more about clinical laboratory studies for early drug development, including the challenges of clinical trials and answers in terms of trial length, sites, measures that are more sensitive, and quality of life issues. The group also discussed looking at translational studies including domain and domain function.